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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,336	01/27/2004	Iontcho R. Vlahov	20150-74359	9879

23643 7590 10/29/2008

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EXAMINER	
JONES, DAMERON LEVEST	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
10/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,336	VLAHOV ET AL.	
	Examiner	Art Unit	
	D. L. Jones	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51,57-65 and 68-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-51,57-65 and 68-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/26/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

ACKNOWLEDGMENTS

1. The Examiner acknowledges receipt of the amendment filed 8/26/08 wherein the specification was amended and claims 1, 26, and 58 were amended; claims 52-56, 66, and 67 were canceled; and claims 68-80 were added. In addition, the Examiner acknowledges receipt of the request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/26/08 has been entered.

Note: Claims 1-51, 57-65, and 68-80 are pending.

RESPONSE TO APPLICANT'S AMENDMENT/ARGUMENTS

2. The Applicant's arguments and/or amendment filed 8/26/08 to the rejection of the claims made by the Examiner under 35 USC 112 have been fully considered and deemed persuasive because Applicant amended and canceled claims to overcome the rejections. Therefore, the said rejections are hereby withdrawn.

CLARIFICATION OF THE REJOINDER PARAGRAPH & REJOINED CLAIMS

3. The Examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or**

otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Notes: Applicant is respectfully requested to review the 'Rejoinder Paragraph' section above. The basis of the rejoinder paragraph is that the product and method/process claims must be of the same scope. This was the basis upon which the Examiner rejoined the product, method, and process claims previously. However, review of the rejoined claims does not illustrate consistency with the product claims and the pending method and process claims. Furthermore, having re-searched the instant invention again, prior art was found which could be used against the product claims. Thus, based on the facts that the process and method claims are not of the same scope and having re-evaluated the claims, a piece of art was found that read on the claims, the restriction is reinstated. However, in the future if the restriction is withdrawn, Applicant is respectively requested to amend the method and process claims to be consistent with the requirements of the rejoinder paragraph above.

Claims 1-4, 7, 16-19, 34, 37, 38, 41, 47, 51, 64, 65, and 79 read on the elected species.

WITHDRAWN CLAIMS

4. Claims 5, 6, 8-15, 20-33, 35, 36, 39, 40, 42-46, 48-50, 57-63, 68-78, and 80 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention/species.

NEW GROUNDS OF REJECTIONS

Double Patenting Rejections

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-4, 7, 16-19, 34, 37, 38, 41, 47, and 79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 1, 2, 4-47, 51, and 52 of copending Application No. 12/064,191. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a composition and uses thereof wherein the composition comprises a receptor binding moiety, a linker and two or more drugs. The claims differ in that those of the instant invention (i.e., claim 1) do not specifically state that two or more drugs may be present in the composition. However, a skilled artisan would recognize that based on claim 37 in the instant invention, a plurality of linkers may be present in the composition which would allow for multiple drugs to be attached. Hence, both 12/064,191 and the instant invention disclose overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 1-4, 7, 16-19, 34, 37, 38, 41, 47, 51, 64, 65, and 79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 6, 9, 12,-16, 20, 31, 41, and 49-51 of copending Application No. 12/064,163. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to compositions and uses thereof wherein the compositions comprise a receptor binding moiety, a linker, and a drug. The claims differ in that those of 12/064,163 are specifically directed to vinca alkaloid drugs wherein the claims of the instant invention read on drugs broadly. Thus, the skilled artisan would recognize that the subject matter of the instant invention encompasses that of 12/064,163.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 1-4, 7, 16-19, 34, 37, 38, 41, 47, 51, and 79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-5, 7-13, 15-22 of copending Application No. 10/513,372. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a receptor binding moiety, a linker, and a drug. The claims differ in that those of 10/513,372 are directed to a specific vitamin binding moiety (folate) and a specific drug (mitomycin). Thus, a skilled artisan would recognize that the claims of the instant invention encompass those of 10/513,372.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

112 First Paragraph Rejections (Written Description)

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-4, 7, 16-19, 34, 37, 38, 41, 47, 51, 64, 65, and 79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is reminded that an Inventor is entitled to a patent to protect his work only if he/she produces or has possession of something truly new and novel. The invention being claimed must be sufficiently concrete so that it can be *described* for the world to appreciate the specific nature of the work that sets it apart from what was before. The Inventor must be able to describe the item to be patented with such *clarity* that the Reader is assured that the Inventor actually has possession and knowledge of the unique composition that makes it worthy of patent protection. The instant application does not sufficiently describe the invention as it relates to the phrases: (a) drug, or an analog, or derivative thereof; (b) vitamin receptor binding analogs and derivatives thereof; (c) amino acid derivative; (d) mitomycin derivative; (e) mitomycin analog; (f) vitamin or an analog or derivative thereof; (g) vinca alkaloid, or an analog or derivative thereof; and (h) vinblastine, vincristine, and analogs and derivatives thereof.

In the instant invention, what the Reader gathers from the instant application is a desire/plan/first step for obtaining a desired result. While the Reader can certainly appreciate the desire for achieving a certain end result, establishing goals does not necessarily mean that an invention has been adequately described.

While compliance with the written description requirements must be determined on a case-by-case basis, the real issue here is simply whether an adequate description of the phrases (a) drug, or an analog, or derivative thereof; (b) vitamin receptor binding analogs and derivatives thereof; (c) amino acid derivative; (d) mitomycin derivative; (e)

mitomycin analog; (f) vitamin or an analog or derivative thereof; (g) vinca alkaloid, or an analog or derivative thereof; and (h) vinblastine, vincristine, and analogs and derivatives thereof are necessary to practice an invention described only in terms of its function and/or based on a disclosure wherein a description of the components necessary in order for the invention to function are lacking. In order to satisfy the written description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the Inventor possessed the claimed invention at the time of filing. In other words, the specification should describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that the Inventor created what is the claimed. Thus, since the specification does not describe the phrases such that one can ascertain the metes and bounds of the instant invention written description requirement is lacking.

112 Second Paragraph Rejections

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-4, 7, 16-19, 34, 37, 38, 41, 47, 51, 64, 65, and 79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims as written are ambiguous because they either depend from claims or themselves contain one or more of the following ambiguous phrases: (a) drug, or an analog, or derivative thereof; (b) vitamin receptor binding analogs and derivatives thereof; (c) amino acid derivative; (d) mitomycin derivative; (e) mitomycin analog; (f)

vitamin or an analog or derivative thereof; (g) vinca alkaloid, or an analog or derivative thereof; and (h) vinblastine, vincristine, and analogs and derivatives thereof.

The phrases are ambiguous because the phrases refer to various groups of compounds generated from parent compounds wherein it is unclear what portion of the parent structure remains in the derivatives. For example, one may generate a derivative by removing a hydrogen or a large portion of the parent structure. One structure would still be a derivative/analog of the other because the parent structure is the same. In addition, a derivative/analog may be generated by, for example, inserting atoms (i.e., heteroatoms) into a parent structure. Hence, the skilled practitioner would not necessarily recognize what composition components Applicant is intending to be compatible with the instant invention. Furthermore, it should be noted that stating that a composition component is generated from a parent structure does not mean that the properties of the resulting analog/derivative is the same/similar to that of the parent. Therefore, the claims as written are vague and indefinite because one cannot readily ascertain what is being claimed.

103 REJECTION

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-4, 7, 16-19, 34, 37, 38, 41, 47, 51, 64, 65, and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briesewitz et al (WO 99/61055) in view of Yang et al (US Patent No. 7,067,111).

Briesewitz et al disclose conjugates of the form Z-L-X wherein Z is a ligand that binds a specific protein; X is a drug moiety; and L is an optional liner (see entire document, especially abstract; page 2, lines 26-29; page 5, lines 16-20; page 7, lines 12-32). The protein ligand and drug moiety may be covalently bonded to each other

directly or through a linking group (page 4, lines 26-28). The term 'drug' as used by Briesewitz et al refers to any active agent that affects a biological processes (page 4, lines 33-36). The drug moiety may contain functional groups such as amines, amides, sulfhydryl, carbonyl, hydroxyl, or carboxyl groups (page 8, lines 3-14). The *drug* moieties are structures found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, *derivatives and structural analogs* or combinations thereof (page 8, lines 15-20). Possible drugs include alkaloids such as ***vinblastine***, vincristine, paclitaxel, daunorubicin, and mitomycin (page 10, lines 18-25). On page 17, lines 17-22, it is disclosed that the ligand may be receptor bind moieties. Page 19, lines 20-26, disclose that the ligand may be vitamins and derivatives thereof (see also, page 49, claim 27). The linking moiety may vary widely depending on the nature of the drug and ligand moieties. The appropriate linkers may readily be identified using the affinity, specificity, or selectivity assays described in the reference. Generally, the linkers will comprise a spacer group that may optionally comprise heteroatoms or may be a ***peptide***. In addition, the spacer group may contain various reactive functionalities such as functional groups (pages 19-20, bridging paragraph). A variety of hosts such as mammals (i.e., humans) may be administered the conjugates of Briesewitz et al. While Briesewitz et al does not specifically disclose folate as the vitamin receptor binding moiety, the reference does disclose the use of vitamin receptor binding agents in combination with linking groups, and a drug.

Yang et al disclose drug delivery conjugates (see entire document, especially, abstract). In column 3, lines 4-42, tissue specific ligands are disclosed. In particular, in

column 3, lines 10-11, it is disclosed that the tissue specific ligand may be a folate targeting receptor agent. Column 3, lines 27-29, disclose that preferred folate receptor targeting ligands include folate. In column 3, lines 45-65, it is disclosed that a linker is typically used to increase drug solubility in aqueous solutions as well as to minimize alteration in the affinity of drugs. The folate conjugate may be radiolabeled (columns 3-4, bridging paragraph; column 13, lines 10-50; columns 16-28, Example 1). In addition, Yang et al (see Example 1, Table 2) disclose that vinblastine is a possible drug to use in combination with the folate targeting agent.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Briesewitz et al using the teachings of Yang et al and generate a composition comprising a folate receptor binding agent, a linker consisting of a peptide, and a drug (a vinblastine derivative) because Briesewitz et al disclose conjugates comprising a linker, drug moiety, and a ligand that binds to proteins (the ligand may be a vitamin receptor binding moiety). Yang et al disclose that folate is a preferred targeting agent that may be conjugated to a linker and drug moiety. In particular, Yang et al (see Table 2) discloses the use of vinblastine as a possible drug that may be used in combination with folate. Therefore, it would have been obvious to a skilled practitioner to generate a composition comprising folate, a peptide linker, and a vinblastine derivative as set forth in Applicant's elected species for the reasons above. Hence, since both Briesewitz et al and Yang et al disclose a vitamin receptor binding agent and a drug agent optionally comprising a linking agent, the references may be

considered to be within the same field of endeavor; thus, the reference teachings are combinable.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (571) 272-0617. The examiner can normally be reached on Mon.-Fri., 6:45 a.m. - 3:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D. L. Jones/
Primary Examiner
Art Unit 1618

October 23, 2008